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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/737,403	12/16/2003	Richard Coale Willson III	015AUS	6655

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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/737,403	WILLSON ET AL.	
	Examiner	Art Unit	
	SAMUEL WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's amendment filed 04/02/2009 and supplemental amendment filed 04/22/2009 have been considered. Presently, claims 1-24 are pending and under consideration.

The double patenting rejection made over application 09/994,701 in the Office action mailed 12/02/2008 is withdrawn in view of the terminal disclaimer filed 04/02/2009.

The objection to claims 6 and 10 made in OA 12/02/2008 is withdrawn in view of Applicant's amendments.

The rejection of claim 10 under 35 U.S.C. 112, 1st paragraph (new matter) made in OA 12/02/2008 is withdrawn in view of Applicant's amendment.

The rejection of claims 1-4, 6, 7, 10 and 22 under 35 U.S.C. 102(b) over Reutelingsberger (US 5, 296, 467) is withdrawn in view of Applicant's amendments to claims 1 and 10 to indicate the desired nucleic acid is DNA (Reutelingsberger exposed bases in RNA, and captured the RNA). While the claims do encompass capture of RNA as an "undesired nucleic acid" in order to separate it from "desired DNA or protein product", since Reutelingsberger did not teach recovering what was not captured (e.g. non-polyadenylated RNA, DNA, proteins, etc), his could not be considered a method for separation of a desired DNA or protein product.

For the same reason, the rejections of claims 14-18, 23 and 24 under 35 U.S.C. 103(a) based on Reutelingsberger are withdrawn.

The rejection of claims 1-4, 6, 8, 10, 11, 14-15, 17 and 21-24 under 35 U.S.C. 103(a) over Colman et al (Eur. J. Biochem. 91:303-310 (1978)) in view of Murphy et al (WO 02/46346398) is maintained for the reasons of record and further explained below. The rejection of claims 7 and 16 is withdrawn as these claims have been amended to depend from claim 5.

The rejection of claim 18 under 35 U.S.C. 103(a) over Colman et al (Eur. J. Biochem. 91:303-310 (1978)) in view of Murphy et al (WO 02/46346398) and further in view of Hawkins (US 5,898,071) is maintained for the reasons of record and further explained below.

The rejection of claims 1-4, 6, 9, 10-12, 14-15, 17 and 20-24 under 35 U.S.C. 103(a) over Birnboim et al (Nucleic Acids Research 7(6):1513-23 (1979)) in view of Murphy et al (WO 02/46346398) is maintained for the reasons of record and further explained below. The rejection of claims 7 and 16 is withdrawn as these claims have been amended to depend from claim 5.

The rejection of claim 18 under 35 U.S.C. 103(a) over Birnboim et al (Nucleic Acids Research 7(6):1513-23 (1979)) in view of Murphy et al (WO 02/46346398) and further in view of Hawkins (US 5,898,071) is maintained for the reasons of record and further explained below.

The rejection of claim 19 under 35 U.S.C. 103(a) over Birnboim et al (Nucleic Acids Research 7(6):1513-23 (1979)) in view of Murphy et al (WO 02/46346398) and further in view of Cohen et al (US 5,945,522) and Cherwonogrodzky et al (US 2001/0055780) is maintained for the reasons of record and further explained below.

The rejection of claims 1, 2, 4, 6, 7, 10 and 14-17 under 35 U.S.C. 102(e) as being anticipated by Willson et al (US 2004/0152076) or alternatively under 35 U.S.C. 102(a) as being anticipated by Murphy et al (WO 02/46398) is withdrawn. The rejection was based on Willson/Murphy teachings single-base mismatch detection, wherein denaturing and reannealing of wildtype and mutant DNA differing at a single base would produce a heteroduplex having a single base mismatch (i.e. a single-stranded region). After further consideration, it is considered unlikely that a duplex with a single base mismatch would produce an "exposed" base such that the disclosed interaction between the base and the immobilized metal atom could occur. Although the mismatched bases would not be expected to form the hydrogen bonds with one another as is the case with matched bases, they would still be expected to be buried within the double helix held together by the flanking matched base sequences.

The rejection of claim 18 over either Willson et al (US 2004/0152076) or Murphy et al (WO 02/46398) in view of Hawkins (US 5,898,071) is withdrawn for the same reasons.

New rejections are set forth below as necessitated by Applicant's amendment.

Previous Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 8, 10, 11, 14-15, 17 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Colman et al (Eur. J. Biochem. 91:303-310 (1978)) in view of Murphy et al (WO 02/46398, prior art of record).

With regard to claims 1 and 10, Colman taught a technique for removing contaminating chromosomal (i.e. host genomic DNA) from plasmid DNA by selective thermal denaturation and renaturation. See page 307, figure 3, panel B and caption: "The sample was then heated at 100 °C for 2 min before rapidly freezing to -70 °C…After thawing to room temperature the sample was immediately subjected to hydroxyapatite chromatography…Tracks (a) and (b) ColE1 from cleared lysate before and after heat denaturation and chromatography, respectively". See also page 308, column 1, last paragraph:

> We have found that the contaminating chromosomal DNA can be completely removed by heat-denaturing the cleared lysate prior to hydroxyapatite chromatography (Fig. 3B, compare tracks a and b). Unfortunately this procedure does not enable superhelical DNA to be resolved from nicked circles (Fig. 3B, tracks a and b).

See also page 309, column 2, first paragraph:

> This contrasting behaviour of the chromosomal and nicked plasmid DNAs might be attributable to the high concentration of complementary plasmid (though not chromosomal) DNA single strands present in the denatured cleared lysate, a situation favouring reassociation.

The principle of Colman's method therefore was to selectively denature and renature the nucleic acids in the lysate, such that the desired nucleic acid (the plasmid) renatured and was retained on the chromatography material (hydroxyapatite), while the undesired nucleic acid (contaminating chromosomal DNA) remained denatured (i.e. in single-stranded form) and therefore passed through the column, thereby separating the desired and undesired nucleic acids.

While the thermal denaturation/renaturation would have inherently exposed purine bases in the undesired nucleic acid (i.e. the chromosomal DNA) by creating single-strandedness, Colman did not teach capture of the desired or undesired nucleic acid by a technique selective for the exposed purine bases.

Murphy taught (page 18):

[0078] The inventors have found that a compound containing a non-shielded purine or pyrimidine moiety or group such as a single-stranded nucleic acid molecule, *e.g.*, an oligonucleotide or an RNA molecule or a molecule including A, G, C, T or U, have affinity to an IMAC matrix; while a compound that does not contain a non-shielded purine or pyrimidine moiety or group or easily accessible aromatic nitrogen on a purine or pyrimidine moiety or group, such as double-stranded DNA, RNA, RNA/DNA complexes, has little or no affinity to the same IMAC matrix. Thus, the inventors have demonstrated that the affinity of immobilized metals toward nucleic acid bases allows the use of IMAC in the separation of double strained nucleic acid polymers from single stranded nucleic acid polymers, the purification of plasmid DNA, RNA, and/or the removal of nucleotides and primers from PCR reactions.

Murphy also taught (page 17):

[0070] The term "non-shielded" means that a purine and/or pyrimidine groups are sufficiently exposed to be able to bind to metal atoms and/or ions immobilized in a matrix, *i.e.*, an IMAC matrix. For example, RNA, co-enzyme A, denatured DNA are all examples of molecules that contain non-shielded purine or pyrimidine moieties or groups. On the other hand, duplex DNA or RNA are examples of shielded molecules containing purine or pyrimidine moieties or groups. Thus, the term non-shielded means a purine or pyrimidine moiety or group sufficiently exposed to be able to bind to a metal and/or ion in an IMAC matrix or ligand.

Murphy also taught (page 46):

[0185] Purification of plasmid DNA is an added advantage of IMAC. Previous work on affinity precipitation of DNA by compaction agents (19) allows for the creation of high purity plasmid preparation without the use of column chromatography. The major contaminant left in the plasmid DNA purified by compaction precipitation is contaminating RNA and linear DNA (1-5%). The IMAC separation technique of this invention is well-suited to bind the remaining RNA (the minor component) and DNA fragments to further purify large quantities of plasmid DNA on relatively small IMAC columns.

Murphy also taught (page 47, emphasis added):

Plasmid and RNA Separation

[0189] The nucleic acid discrimination achieved with IMAC suggests application of the method to the purification of plasmid DNA from RNA-rich bacterial lysates. Figure 8 illustrates repeated batch stripping of 1 mL of an alkaline lysate of *E. coli* JM109 containing pBGS19luxwt plasmid with 50 mL of Cu(II)-charged IDA Sepharose per mL of lysate. Control lane 2 shows a lysate after exposure to uncharged IDA Sepharose, showing that the interactions are strictly dependent on the presence of metal ions. Lanes 5-8 trace one supernatant repeatedly exposed to Cu (II) charged IDA Sepharose. The RNA is effectively removed without loss of the closed circular plasmid. The linearized plasmid is also gradually removed, presumably through interactions with damaged, single-stranded regions.

Murphy also taught that one application of his method was "Plasmid DNA with reduced content of nicked and linearized forms" (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Colman by substituting the hydroxyapatite chromatography with IMAC chromatography as taught by Murphy, since Murphy's technique provides a clear advantage over that of Colman. Colman lamented that his technique did not resolve superhelical plasmid from nicked circles (see text cited above), whereas Murphy's method offered the advantage of plasmid DNA with a reduced content of nicked (and linearized) forms. In making this modification, one would have been motivated to retain the selective thermal denaturation/renaturation step taught by Colman, since Murphy taught that denatured DNA contains non-shielded bases subject to separation by IMAC chromatography (see paragraphs [0070] and

[0078] cited above). Furthermore, it is clear that IMAC is selective for exposed purine bases, based on the data shown in figure 3 and discussed in paragraph [0056], which indicates IMAC has stronger affinity for As and Gs (purines) than Cs and Ts (pyrimidines). Finally, Murphy expressly suggests using IMAC for plasmid purification (paragraph [0185]).

With regard to claims 2 and 4, by carrying out the thermal denaturation renaturation step taught by Colman, followed by IMAC chromatography taught by Murphy, one would inherently introduce single-strandedness (thereby exposing purine bases) in contaminating RNA and host genomic (i.e. chromosomal) DNA.

With regard to claim 3, plasmid preparations are sensitive to host genomic DNA contamination during selective separation (which is why Colman expressed an interest in removing it).

With regard to claims 6 and 14, by carrying out the thermal denaturation renaturation step taught by Colman, followed by IMAC chromatography taught by Murphy, one would inherently conduct IMAC chromatography, which involves the use of chelated metal (Murphy page 2, paragraph [0005]).

With regard to claim 8, the denaturation/renaturation taught by Colman involved rapidly cooling the sample comprising the contaminating chromosomal DNA to below 65 °C (see caption of figure 3: "rapidly freezing to -70 °C").

With regard to claim 11, Colman expresses the sentiment that nicked plasmid is undesirable (page 308, column 1, last paragraph). Murphy taught his method produced

plasmid DNA with a reduced content of nicked and linear forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").

With regard to claim 15, Murphy taught multi-channel plates ("well plate"; page 12, Table A, Parameter: Support Shape).

With regard to claim 17, Murphy taught (page 21, paragraph [0089]): "The present invention also relates to a magnetic object such as a bead, stirring rod, or the like either coated with an IMAC ligand or where the object has a porous outer surface to which an IMAC ligand has been bonded to, deposited thereon or therein. The present invention also relates to the use of these magnetic objects to batch-wise purify samples containing target single stranded nucleic acid sequences such as RNAs, oligonucleotides, or the like where the single stranded nucleic acid sequences bind to the magnetic object, which can then be removed from the solution, washed free of contaminates and eluted to recover the single stranded nucleic acid sequences."

With regard to claims 21 and 22, by carrying out the thermal denaturation renaturation step taught by Colman, followed by IMAC chromatography taught by Murphy, one would inherently capture contaminating genomic DNA and RNA.

With regard to claim 23, Murphy taught HIC (hydrophobic interaction chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").

With regard to claim 24, Murphy taught RPC (reverse phase chromatography; "Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Colman et al (Eur. J. Biochem. 91:303-310 (1978)) in view of Murphy et al (WO 02/46398, prior art of record) as applied to claims 1-4, 6, 8, 10, 11, 14-15, 17 and 21-24 above, and further in view of Hawkins (US 5,898,071).

The teachings of Colman and Murphy have been discussed. These references did not teach processing multiple samples in parallel.

Hawkins taught methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel" (column 10, lines 54-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method suggested by the combined teachings of Colman and Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.

Response to Arguments

Applicant's arguments filed 04/22/2009 have been fully considered but they are not persuasive. Applicant argues (pages 15-16) of the response: "Claims 1 and 10 have now been amended to more clearly recite the release of the desired DNA or protein product prior to exposing the purine base handles by creating single-stranded regions. This distinguishes over the Murphy and Colman references." It is unclear if the emphasis on "by creating single-stranded regions" was intended to be a distinguishing feature over the cited art, or whether the underlining left over from the amendment. In

any case, Applicant appears to be arguing two distinguishing elements: the "releasing of the desired DNA or protein product" (i.e. the "lysing any cell within which the desired product is contained") and the "by creating single-stranded regions". Neither of these distinguishes over the cited art.

With regard to the "lysing" limitation, it is respectfully submitted that the language "lysing any cell within which the desired product is contained" only requires the lysing step in the case that the desired product is contained within a cell. The claims themselves do not require that the desired product is contained within a cell. If Applicant wishes this to be a requirement of the claim (i.e. that the desired product is within a cell, and that the claimed method requires lysing said cell), then the claim language should directly recite this. As set forth in MPEP 2106(II)(C): "Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation." So, in the case where a prior art reference separates a desired DNA or protein product, unless that product is inside a cell, the prior art reference need not teach lysing the cell, because the language of the claim requires lysis only in the case of products within cells. In other words, "lysing any cell within which the desired product is contained" is construed as "if the desired DNA or protein product is contained within a cell, lysing said cell".

However, in the case of the rejections based on Colman, Colman taught that the desired DNA product (plasmids) were contained in cells of E. coli (page 303, column 2, "Table 1 shows the bacterial strains used, their source, the plasmids they contain...").

In addition, Colman clearly taught lysing these cells (page 304, column 1, first paragraph, "The plasmids pXI212, pXI108 and XIr101 all contain inserts of *Xenopus laevis* ribosomal DNA. Their host bacterial strains were grown and lysed..."). Therefore, the "lysing" limitation does not distinguish over Colman.

As to the other limitation in question, "by creating single-stranded regions", as described in the rejection over Colman, the thermal denaturation/renaturation used by Colman would have inherently exposed purine bases in the undesired nucleic acid (i.e. the chromosomal DNA) by creating single-strandedness, and one would have been motivated to retain this denaturation/renaturation step when substituting Murphy's IMAC column for Colman's hydroxyapatite column because Murphy taught that denatured DNA contains non-shielded bases subject to separation by IMAC chromatography (see paragraphs [0070] and [0078]).

Applicant's arguments for claim 18 rely on the same reasoning and are therefore similarly unpersuasive.

Claims 1-4, 6, 9, 10-12, 14-15, 17 and 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birnboim et al (Nucleic Acids Research 7(6):1513-1523 (1979)) in view of Murphy et al (WO 02/46398, prior art of record).

With regard to claims 1 and 10, Birnboim taught a method for purifying plasmid DNA wherein nucleic acids in a cell lysate are selectively denatured under alkaline conditions (see page 1514, "Principle of the alkaline extraction method"). Such alkaline denaturation (i.e. the separation of the two strands of double-stranded DNA) would

inherently expose purine (as well as pyrimidine) bases by creating single-strandedness. Birnboim did not teach capturing the desired or undesired nucleic acid product by a technique selective for the exposed purine bases and separation of the desired and undesired nucleic acids.

Birnboim's method resulted in plamid DNA contaminated with a number of undesirable nucleic acids (see paragraph bridging pages 1518-1519 and figure 1, lane e). These included "irreversibly denatured" plasmid DNA, contaminating chromosomal DNA, low molecular weight RNA, and nicked plasmid DNA (i.e. open circular or "OC" DNA).

Murphy taught (page 18):

> **[0078]** The inventors have found that a compound containing a non-shielded purine or pyrimidine moiety or group such as a single-stranded nucleic acid molecule, *e.g.*, an oligonucleotide or an RNA molecule or a molecule including A, G, C, T or U, have affinity to an IMAC matrix; while a compound that does not contain a non-shielded purine or pyrimidine moiety or group or easily accessible aromatic nitrogen on a purine or pyrimidine moiety or group, such as double-stranded DNA, RNA, RNA/DNA complexes, has little or no affinity to the same IMAC matrix. Thus, the inventors have demonstrated that the affinity of immobilized metals toward nucleic acid bases allows the use of IMAC in the separation of double strained nucleic acid polymers from single stranded nucleic acid polymers, the purification of plasmid DNA, RNA, and/or the removal of nucleotides and primers from PCR reactions.

Murphy also taught (page 17):

[0070] The term "non-shielded" means that a purine and/or pyrimidine groups are sufficiently exposed to be able to bind to metal atoms and/or ions immobilized in a matrix, *i.e.*, an IMAC matrix. For example, RNA, co-enzyme A, denatured DNA are all examples of molecules that contain non-shielded purine or pyrimidine moieties or groups. On the other hand, duplex DNA or RNA are examples of shielded molecules containing purine or pyrimidine moieties or groups. Thus, the term non-shielded means a purine or pyrimidine moiety or group sufficiently exposed to be able to bind to a metal and/or ion in an IMAC matrix or ligand.

Murphy also taught (page 46):

[0185] Purification of plasmid DNA is an added advantage of IMAC. Previous work on affinity precipitation of DNA by compaction agents (19) allows for the creation of high purity plasmid preparation without the use of column chromatography. The major contaminant left in the plasmid DNA purified by compaction precipitation is contaminating RNA and linear DNA (1-5%). The IMAC separation technique of this invention is well-suited to bind the remaining RNA (the minor component) and DNA fragments to further purify large quantities of plasmid DNA on relatively small IMAC columns.

Murphy also taught (page 47, emphasis added):

Plasmid and RNA Separation

[0189] The nucleic acid discrimination achieved with IMAC suggests application of the method to the purification of plasmid DNA from RNA-rich bacterial lysates. Figure 8 illustrates repeated batch stripping of 1 mL of an alkaline lysate of *E. coli* JM109 containing pBGS19luxwt plasmid with 50 mL of Cu(II)-charged IDA Sepharose per mL of lysate. Control lane 2 shows a lysate after exposure to uncharged IDA Sepharose, showing that the interactions are strictly dependent on the presence of metal ions. Lanes 5-8 trace one supernatant repeatedly exposed to Cu (II) charged IDA Sepharose. The RNA is effectively removed without loss of the closed circular plasmid. The linearized plasmid is also gradually removed, presumably through interactions with damaged, single-stranded regions.

Murphy also taught that one application of his method was "Plasmid DNA with reduced content of nicked and linearized forms" (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Birnboim by subjecting the alkaline lysate to IMAC chromatography as taught by Murphy, since Murphy's technique provides a clear advantage over that of Birnboim. Murphy's method offered the advantage of plasmid DNA with a reduced content of nicked (and linearized) forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product"). Furthermore, Murphy expressly suggests applying IMAC to alkaline cell lysates in order to remove RNA and linearized plasmid (paragraph [0189]). Furthermore, it is clear that IMAC is selective for exposed purine bases, based on the data shown in figure 3 and discussed in paragraph [0056], which indicates IMAC has stronger affinity for As and Gs (purines) than Cs and Ts (pyrimidines).

With regard to claims 2 and 4, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently introduce single-strandedness (thereby exposing purine bases) in contaminating RNA and host genomic (i.e. chromosomal) DNA.

With regard to claim 3, plasmid preparations are sensitive to host genomic DNA contamination during selective separation.

With regard to claims 6 and 14, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would

inherently conduct IMAC chromatography, which involves the use of chelated metal (Murphy page 2, paragraph [0005]).

With regard to claim 9, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently conduct an alkali based process in which genomic DNA or other nucleic acid contaminant was rapidly neutralized and captured by an affinity method (see Birnboim, page 1514, "Principle of the alkaline extraction method").

With regard to claims 11 and 12, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently remove undesired open circular (i.e. nicked) and linear plasmid DNA from supercoiled plasmid DNA. Murphy taught his method produced plasmid DNA with a reduced content of nicked and linear forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product").

With regard to claim 15, Murphy taught multi-channel plates ("well plate"; page 12, Table A, Parameter: Support Shape).

With regard to claim 17, Murphy taught (page 21, paragraph [0089]): "The present invention also relates to a magnetic object such as a bead, stirring rod, or the like either coated with an IMAC ligand or where the object has a porous outer surface to which an IMAC ligand has been bonded to, deposited thereon or therein. The present invention also relates to the use of these magnetic objects to batch-wise purify samples containing target single stranded nucleic acid sequences such as RNAs, oligonucleotides, or the like where the single stranded nucleic acid sequences bind to

the magnetic object, which can then be removed from the solution, washed free of contaminates and eluted to recover the single stranded nucleic acid sequences."

With regard to claim 20, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently capture linear plasmid DNA. Murphy taught his method produced plasmid DNA with a reduced content of nicked and linear forms (page 11, Table A, under column entitled "Preferred" and row entitled "DNA product"); see also paragraph [0189].

With regard to claims 21 and 22, by carrying out the alkaline denaturation step taught by Birnboim, followed by IMAC chromatography taught by Murphy, one would inherently capture contaminating genomic DNA and RNA.

With regard to claim 23, Murphy taught HIC (hydrophobic interaction chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").

With regard to claim 24, Murphy taught RPC (reverse phase chromatography; "Reverse Phase Resin", which implicitly teaches reverse phase chromatography; page 12, Table A, column 3, row beginning "2nd Zone Other Constituents").

Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birnboim et al (Nucleic Acids Research 7(6):1513-1523 (1979)) in view of Murphy et al (WO 02/46398, prior art of record) as applied to claims 1-4, 6, 9, 10-12, 14-15, 17 and 20-24 above, and further in view of Hawkins (US 5,898,071).

The teachings of Birnboim and Murphy have been discussed. These references did not teach processing multiple samples in parallel.

Hawkins taught methods of nucleic acid purification and teaches that an "advantage of using a microtiter plate is that many samples can be isolated in parallel" (column 10, lines 54-60).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the method suggested by the combined teachings of Birnboim and Murphy to process multiple samples in parallel, because Hawkins teaches this to be advantageous.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Birnboim et al (Nucleic Acids Research 7(6):1513-1523 (1979)) in view of Murphy et al (WO 02/46398, prior art of record) as applied to claims 1-4, 6, 9, 10-12, 14-15, 17 and 20-24 above, and further in view of Cohen et al (US 5,945,522) and Cherwonogrodzky et al (US 2001/0055780).

The teachings of Birnboim and Murphy have been discussed. In particular, it was explained in the discussion of claim 20 as to how one would have arrived capturing linear plasmid DNA. The Birnboim and Murphy disclosures did not teach or suggest copying BACs, PACs or YACs, which are particular species of large plasmids.

Cohen taught purifying BAC DNA by alkaline lysis of cells followed by centrifugation on cesium chloride gradient to obtain purified BAC DNA (column 15, lines

45-50). Birnboim also discusses cesium chloride centrifugation to separate closed circular plasmid DNA from open circular or linear DNA (page 1513, "Introduction").

Cherwonogrodzky taught that cesium chloride centrifugation was costly and time consuming (paragraph [0061]).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method suggested by the combined teachings of Birnboim and Murphy to purify BAC DNA, which would inherently result in capturing linear BAC DNA on the IMAC material. One would have been motivated to purify BAC DNA since Cohen evidences that purification of BAC DNA was desired in the prior art, and one would have been motivated to use Murphy's IMAC technique instead of Cohen's cesium chloride technique because Cherwonogrodzky taught that the latter approach was costly and time consuming. Murphy taught, on the contrary, that "IMAC worked well as a fast and efficient means of stripping RNA from a plasmid containing lysates" ([*sic*], page 46, paragraph [0187]). Murphy also taught the IMAC approach removed linear plasmid DNA (paragraph [0189]). Hence, by purifying BAC DNA according to the combined teachings of Birnboim and Murphy, one would have inherently captured linear plasmid (BAC) DNA.

Response to Arguments

Applicant's arguments filed 04/22/2009 have been fully considered but they are not persuasive. Applicant argues (page 19) of the response: "Birnboim does not teach the use of selective denaturation for changing the conformational state of gDNA to allow selective separation from plasmid DNA per the Specification para 0011. Combining

Birnboim and Murphy still does not read on applicants' three step process of liberation, exposure and capture."

As an initial matter, it does not matter whether the prior art teaches what is recited in paragraph 0011 of the instant specification unless it is also recited in the claims.

With regard to the "lysing" limitation (i.e. "liberation" as Applicant uses in this argument), it is respectfully submitted that the language "lysing any cell within which the desired product is contained" only requires the lysing step in the case that the desired product is contained within a cell. The claims themselves do not require that the desired product is contained within a cell. If Applicant wishes this to be a requirement of the claim (i.e. that the desired product is within a cell, and that the claimed method requires lysing said cell), then the claim language should directly recite this. As set forth in MPEP 2106(II)(C): "Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation." So, in the case where a prior art reference separates a desired DNA or protein product, unless that product is inside a cell, the prior art reference need not teach lysing the cell, because the language of the claim requires lysis only in the case of products within cells. In other words, "lysing any cell within which the desired product is contained" is construed as "if the desired DNA or protein product is contained within a cell, lysing said cell".

However, in the case of the rejections based on Birnboim, Birnboim taught that the desired DNA product (plasmids) were contained in cells of E. coli (see abstract: "A

procedure for extracting plasmid DNA from bacterial cells..."). In addition, Birnboim clearly taught lysing these cells (page 1514, "Principle of the Alkaline Extraction Method"). Therefore, the "lysing" limitation does not distinguish over Birnboim. To the extent that the word "thereafter" in the claim limitation "thereafter exposing purine bases present" implies an order of steps, it is submitted that treating the cells with an SDS/NaOH solution would have lysed the cells immediately prior to the denaturation (the creation of single-strandedness) of the DNA within. That is, the NaOH (which produced the alkaline conditions causing DNA denaturation) would not have been able to effect DNA denaturation until the cell had been lysed (by the SDS) since the DNA would not have been exposed to the NaOH until cell lysis had occurred. Were the SDS not present in Birnboim's solution, it is possible that the NaOH could have gradually diffused into the cells to cause an intracellular alkaline environment resulting in DNA denaturation without lysing the cells. However, since Birnboim's solution did contain SDS, the cells would have been immediately lysed, even if only seconds (or milliseconds) before the alkaline denaturation of the DNA inside. Hence, the exposing of purine bases caused by alkaline denaturation occurred after the cell lysis in Birnboim's method.

Therefore, Birnboim taught lysing, and thereafter exposing purine bases in undesired nucleic acid (i.e. chromosomal DNA, RNA, nicked plasmids) by creating single-strandedness through alkaline denaturation. Muphy's disclosure provides for the capturing by a technique selective for purine bases (i.e. IMAC).

Applicant's arguments for claims 18 and 19 rely on the same reasoning and are therefore similarly unpersuasive.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant has amended claim 1 to recite "of a desired DNA or protein product" in line 2, but then refers to "the desired nucleic acid product" in lines 5-6 and 10 of the claim. These latter instances of "the desired nucleic acid product" should be changed to "the desired DNA product". Because claims 2-4, 6, 8, 9, 11-15 and 17-24 depend from claim 1, they are rejected for the same reason.

Likewise, claim 4, which depends from claim 1, recites "wherein the captured nucleic acid product" should be changed to "wherein the captured DNA product". Applicant may also consider "wherein the captured DNA product or undesired nucleic acid".

Claim 5 recites "A scalable process for the highly selective, high yield separation of a desired recombinant polymerase from undesired nucleic acid", and then immediately thereafter recites "exposing purine bases present within either the desired nucleic acid product or undesired nucleic acid...". The "desired product" is a

recombinant polymerase, not a nucleic acid. Likewise, "capture of the desired nucleic acid product..." does not belong in this claim. The "desired product" is a recombinant polymerase, not a nucleic acid. Because claims 7 and 16 depend from claim 5, they are rejected for the same reason.

Applicant has amended claim 10 to recite "of a desired DNA or protein product" in line 2, but then refers to "the desired nucleic acid product" in lines 5-6 and 10 of the claim. These latter instances of "the desired nucleic acid product" should be changed to "the desired DNA product".

Conclusion

Claims 5, 7 and 16 are free of the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637

/Young J Kim/
Primary Examiner, Art Unit 1637